The plasma membrane calcium pumps: learning from disease-causing mutations

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The Ca^{2+} ATPases of the plasma membrane (PMCA pumps) play a fundamental role in controlling the homeostasis of Ca^{2+} in all eukaryotic cells. In mammals they are encoded by four separate genes: PMCA1 is ubiquitous and has a housekeeping role; PMCA4 is also ubiquitous but exerts tissue-specific roles; PMCA2 and PMCA3 are tissue-restricted, with high levels of expression in neurons. The number of PMCA isoforms is greatly increased by alternative splicing of the primary transcripts. The three-dimensional structure of the PMCA pump has not been solved, but molecular modelling on SERCA pump templates reveals that the PMCA pump is settled in the plasma membrane with ten transmembrane helices, two main cytosolic loops and a long C-terminal cytosolic tail. The second loop contains the catalytic center, while the C-terminal domain is bound to the main body of the pump in the resting state, keeping PMCA autoinhibited. When calmodulin is present, it interacts with high affinity with the C-terminal tail, activating the pump. PMCA is also regulated by acidic phospholipids, kinases, dimerization and a series of protein partners. The pump coexists with much more powerful systems that clear Ca^{2+} from the bulk cytosol, but is essential for the handling of Ca^{2+} signals in selected sub-plasma membrane microdomains. PMCA dysfunctions, frequently linked to genetic mutations, are responsible for a plethora of pathologies, the ones related to the neurons-restricted isoforms being the best characterized. Functional analysis revealed a tightly regulated threshold of intracellular Ca^{2+} to be fine-tuned in order to avoid the disease onset.